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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,907	02/25/2004	Bjarne Bogen	2600-000003	6743

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HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 828
BLOOMFIELD HILLS, MI 48303

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/786,907	BOGEN ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,77 and 83-130* is/are pending in the application.

4a) Of the above claim(s) *1-37,77,84-87,93,94,101-108 and 127-130* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83, 88-92, 95-100 and 109-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Claims 1-37 and 77 are withdrawn and Claims 38-76 and 78-82 cancelled by amendment in the Reply of September 11, 2006. New claims 83-130 were added by amendment and Applicant's identification of original written description support for the new claims cited on p. 17, ¶1 to p. 20, ¶3 has been considered, and new claims 83-130 have been entered.

Election/Restrictions

2. Applicant's election with traverse of Group IV in the reply filed on September 11, 2006 is acknowledged. The traversal is on the ground(s) that the subject matter of Group IV (new claims 83-123) and Group VI (new claims 124-126) should be rejoined because "all the claims share the operative feature of being or comprising nucleic acid of original Claim 38" (p. 14-16). Applicant's arguments are found persuasive because the vaccine composition (Claims 124-130) comprises the same nucleic acid of Claim 83. The restriction of Groups IV and VI is withdrawn.

3. Applicant's election of the species in the reply filed on September 11, 2006 is acknowledged. For the species restriction of the nucleic acid claims, Applicants have provisionally elected a) targeting units for a ligand (p. 21, Item 13A), a chemokine for a ligand (p. 22, Item 13B) and MIP-1α for a chemokine (p. 22, Item 13D) and b) an antigenic scFV for the antigenic units. For the species restriction of the vaccine claims, Applicants have provisionally elected a cancer vaccine composition. Because applicant did not distinctly and specifically point out the supposed errors in the election of species

requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Nevertheless, the Examiner has withdrawn the species restriction for the targeting ligand to include soluble CD40 ligand and the RANTES chemokine.

Applicants have requested that they be allowed to elect targeting units that have the ability to target APC (p. 21, Item 13A), however, Claim 95 of elected Group IV is drawn to the targeting units having the ability to target APCs.

4. Claims 84-87, 93, 94, 101-108 and 127-130 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species, there being no allowable generic or linking claim.

5. Claims 83, 88-92, 95-100 and 109-126 are all the pending claims under examination with targeting units for a ligand comprising the species to soluble CD40 ligand and the chemokines RANTES and MIP-1α and antigenic units for an antigenic scFv.

Information Disclosure Statement

6. The international patent reference and the non-patent literature references cited in the IDS of September 14, 2004 have been considered and entered.

Sequence Compliance

7. Pursuant to 37 CFR 1.821(c), a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more

nucleotides. The specification contains the following primer sequences and linker sequence, and for which no sequence listing has been provided:

primers- p. 20, [0049]; p. 21, [0050-0051]; p. 22, [0052]; p. 22-24, [0054]; p. 24, [0056] and p. 39, [00105]; and

linker- [0029] and figures 8-11.

Applicants are required to provide a Sequence Listing, a computer readable form of the Sequence Listing and a statement under 37 C.F.R. 1.821-1.825. Please see the attached Notice to Comply Form, for which the Examiner has set a 3-month shortened statutory period for response. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Specification

8. The specification is objected to because it does not provide sequence identifiers for the following primer sequences and linker sequence pursuant to 37 CFR 1.821 (c) and/or (d):

primer- p. 20, [0049]; p. 21, [0050-0051]; p. 22, [0052]; p. 22-24, [0054]; p. 24, [0056] and p. 39, [00105]; and

linker- [0029] and figures 8-11.

Applicants are required to identify the sequences referred to in each of the foregoing paragraphs or respective figure legends with sequence identifiers in addition to any other sequences that may not be properly identified.

9. In [0038], there appears to be a typographical error: "C□3" should be "Cγ3".

10. The use of the trademarks, e.g., TRIzol® and pGEM®-T Easy Vector have been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

11. Claims 96, 97 and 124-126 are objected to as being drawn to non-elected subject matter for the species HLA, CD14 and a toll-like receptor (claim 96), a subspecies HLA-DP (claim 97) and an infectious disease (claims 124-126).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 91, 100, 110, 113, 114, 121 and 124-126 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 91 is indefinite for the recitation "MIP-1α" as the term encompasses any chemokine protein. Amending the claim to recite "Macrophage Inflammatory Protein 1 alpha" would overcome the rejection.

b) Claims 100, 110 and 114 are indefinite for the recitation "derived". The term "derived" is not one which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of a ascertainable meaning for said phrase. Since it is unclear how the hinge regions are to be derivatized to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Further, it is not clear whether the "derived" hinge is formed by attachment of a detectable marker, therapeutic molecule, some other molecule or altering the amino acid sequence, for examples. In addition, since the term "derived" does not appear to be clearly defined in the specification, and the term can encompass proteins with amino acid substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

c) The term "substantially" in claim 113 is a relative term which renders the claim indefinite. The term "substantially " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. One skilled in the art cannot determine from the specification what percent degree of homology or identity should be shared between the sequence and the C domain in order for the homology to be substantial. The specification does not define the term "substantial".

d) Claims 121 and 124-126 are indefinite for the recitation "degenerate variant thereof" because in Claims 121 and 124, the phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification does not define the terms "degenerate" or "variant" or what comprises a "degenerate variant". Does the term "degeneracy" refer to the degeneracy of the genetic code for the nucleic acids that would encode the same antibody based molecule?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 118, 121, 122 and 124-126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a recombinant antibody-based molecule, wherein said antibody-based molecule comprises two targeting units and two antigenic units that are connected through a dimerization motif, does not reasonably provide enablement for a) administering the nucleic acid to a patient for inducing production of the molecule (Claim 118) or b) pharmaceutical compositions comprising vectors encoding the nucleic acid (Claim 121) or host cells comprising the vectors (Claim 122) where the intended use is to induce a protective immune response against cancer such as myeloma or lymphoma in a patient or c) vaccines comprising the nucleic acid for preventing cancer such as myeloma or

lymphoma in a patient (Claims 124-126). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Claim 118 is drawn to a nucleic acid encoding a recombinant antibody-based molecule, wherein said antibody-based molecule comprises two targeting units and two antigenic units that are connected through a dimerization motif and the nucleic acid is formulated for administration to a patient to induce production of the recombinant antibody-based molecule. Claims 121 and 122 are drawn a pharmaceutical composition comprising a nucleic acid or a degenerate variant thereof or a vector or a cell transfected with the vector encoding the recombinant antibody-based molecule, in combination with a physiologically acceptable diluent or carrier. Claims 124-126 are drawn to a vaccine composition against cancer, comprising an immunologically effective amount of the nucleic acid or a degenerate variant thereof, wherein said composition is able to trigger both a T-cell- and B-cell immune response.

Claims 118, 121 and 122 are drawn to products having an intended use for inducing an immune response against a cancer. The claims encompass any cancer using a nucleic acid which must be expressed in order to produce an immuno-effective amount of recombinant antibody-based molecule.

The specification teaches treating multiple myeloma or lymphoma in a patient using the nucleic acid molecules encoding a human antibody-based molecule, production of vaccibodies in serum after injection of DNA intramuscularly and in vivo electroporation of BALB/c mice (Example 4 [0092]; FIG. 21); production of anti-Id antibodies in serum after injection of vaccibody DNA intramuscularly and electroporation (Example 5 [0094]); and induction of protective immunity against the MOPC315.4 myeloma challenge in BALB/c mice by vaccibody DNA injection/electroporation (Example 6 [0096]). In all of the working examples for the mouse model, "electroporation was performed by applying rod electrodes to the skin near the site of the injection and subjecting the site to an electrical potential comprising 10 trains of 1000 pulses each, with a pulse length at two times 200 Sec (positive 200Sec and negative 200 Sec) with 600 s interval between each pulse and with a current limit of 50 mA (about 150-174 V/cm) (Tollefsen et al. Vaccine 20(27-28):3370-8 (2002))" [0077-0078].

The specification does not teach methods of treating or preventing a cancer much less a myeloma or lymphoma or inducing a protective T- or B-cell immune response in a patient with the nucleic acid, the vector comprising the nucleic acid or a vector-transfected cell or cell line encoding the recombinant antibody-based molecule.

There are no working examples in Applicant's specification to guide the skilled artisan in practicing the administration of the nucleic acid, vector or transfected host cell, more especially by injection and electroporation, which results in a) induction of an immune B- and T cell response or b) a reduction in a cancer such as myeloma or lymphoma. In addition, one cannot extrapolate the teaching of the specification to the claimed invention because the specification provides no exemplification of or guidance on how to use the claimed nucleic acid, pharmaceutical compositions or vaccine formulation for active immunotherapy or immunoprevention in humans. The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease.

The state of the art for cancer gene therapy as discussed by Vile et al (Gene Therapy, Vol. 7, pp. 2-8, 2000) is unpredictable. Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the

bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

In addition, Rochlitz C. F. (Swiss Medicine Weekly, 131:4-9, 2001) teaches:

"that none of the more than one hundred clinical studies performed so far had formally proven efficacy of the approach [gene therapy] in any human disease. Although anecdotal reports of tumor responses are becoming more frequent in several human malignancies, the situation has not changed dramatically." (See page 8, bottom of page). Rochlitz continue "Main problems are still the lack of vectors with high transduction efficiency in vivo, the low tumor specificity of available systems, and our incomplete knowledge of molecular tumor pathology." (see pages 8-9).

Thus, at the time the application was filed, the state of the art for gene therapy was considered highly unpredictable.

Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) would result in a therapeutic response using the nucleic acid, recombinant vector and vector transfected host cell encoding the recombinant antibody-based molecule. The state of the art for the route of administration for gene therapy as exemplified by Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

Therefore, the skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant

invention pertains. Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

In view of the lack of predictability of the art to which the invention pertains, the lack of established clinical protocols for effective cancer therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for decreasing the volume of solid tumors in a patient, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 83, 88-92, 96, 98, 109-117, 119, 120 and 123 are rejected under 35 U.S.C. 102(e) as being anticipated by Herman (US 20050069549; published March 31, 2005; filed Jan 14, 2003).

Claims 83, 88-92, 95, 96, 98-100, 109-117, 119, 120 and 123 are drawn to a nucleic acid encoding a recombinant antibody-based molecule, wherein said antibody-

based molecule comprises two targeting units and two antigenic units that are connected through a dimerization motif, where the targeting agent is a ligand comprising soluble CD40 ligand or a chemokine such as RANTES or MIP-1α, where the targeting units target APCs, and have the ability to target CD40 and chemokine receptors, and the antigenic units is an antigenic scFv derived from a monoclonal Ig produced by a myeloma or lymphoma, where the dimerization motif is a hinge region and an Ig domain, the hinge derived from the Ig, the hinge forming one or several covalent bonds or a disulphide bridge, where the Ig domain is a carboxyterminal C domain and derived from IgG, and the Ig domain can homodimerize by non-covalent interactions such as hydrophobic interactions, and vectors comprising the nucleic acid, and host cells transfected with the vectors and a kit comprising the nucleic acid to produce the antibody-based molecule.

Herman discloses nucleic acids, vectors comprising nucleic acids and vector transfected host cells encoding a multispecific ligand comprising at least two different binding specificities for different target ligands comprising any combination of one or more antibody fragments or recombinant reconstructions (scFvs) of antibodies including tetraspecific antibody formats and fusions of the antibody to other functional moieties (eg. toxins, cytokines, chemokines, streptavidin, adhesion molecules) [0107-0108], where the multispecific ligand comprises comprise an Fc portion and a hinge portion and that one or both of a) the length, amino acid composition or molecular weight (or various combinations of these interrelated factors) of the Fab or Fc portion; and b) the amino acid composition (including length) of the hinge portion (eg. any polypeptide

segment that provides means for linking two typically heavy chains, eg. through one or more disulfide bonds, leucine zipper, fos-jun, optionally a flexible hinge typical of an IgG1 or having one to several more disulfide bonds eg. IgG3) [0116]. The binding characteristics of the multispecific ligand include a multispecific ligand in which neither target ligand is of sufficient affinity in the circumstances to effectively (with effect) bind or remain bound without the other target ligand being available for simultaneous binding [0119]; and a first ligand moiety which recognizes a first target ligand that is over-expressed on a disease associated entity for example a diseased or disease-causing or mediating cell or infectious agent and a second ligand binding moiety that recognizes a target ligand and wherein the first target ligand is characterized in that it does not lend itself to facilitating or permitting internalization of the second ligand binding moiety [0122]. Herman discloses the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety that binds to a ligand which effects binding to another immune cell, for example a T cell or APC or the multispecific ligand is a tetraspecific antibody or the first moiety binds to but is incapable of modulating the activity of an immune cell and the second moiety modulates the activity of the immune cell independently of the first moiety [0137]. Herman discloses a multispecific ligand which comprises a first ligand binding moiety which neutralizes a ligand eg. a natural ligand such as a chemokine and a second ligand binding moiety which binds to a cell marker associated with a cell [0138]. Examples of proteins which are targeted by multispecific ligand (targeting unit) include CD40 [0164], MIP-1 alpha and RANTES [0428]. Herman discloses a multispecific ligand comprising an anti-idiotype antibody (antigenic unit) so

as to facilitate a desired immune response eg. vaccination type responses [0172, 0252]. For one embodiment, Herman discloses a multispecific ligand containing an immunocytokine containing an anti-idiotypic antibody component and a cytokine component [0018]. Herman discloses nucleic acids, expression vectors and host cells expressing the vectors to produce a multispecific ligand [0241- 0298; 0314-0319]. Herman discloses a kit comprising one or more polynucleotides comprising one or more DNA sequences, where the DNA sequences encode one or more polypeptides which are sufficient to constitute a multispecific ligand as defined in any of the preceding paragraphs [0424].

Because Applicants have not limited the nucleic acid to any physical organization with respect to orientation amongst the two targeting units, two antigenic units and the dimerization motif, the claims are anticipated by the multispecific ligand of Herman.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	Application No. 10/786,907	Applicant(s) Bogen et al.	
	Examiner Lynn Bristol	Art Unit 1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

Pursuant to 37 CFR 1.821(c), a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. The specification contains the following primer sequences and linker sequence, and for which no sequence listing has been provided:

primers- p. 20, [0049]; p. 21, [0050-0051]; p. 22, [0052]; p. 22-24, [0054]; p. 24, [0056] and p. 39, [00105]; and

linker- [0029] and figures 8-11.